REMARKS

Upon entry of this Amendment, claims 23 to 32 will be pending in this application, of which claims 23 and 24 are independent.

The claims stand rejected under 35 U.S.C. §112, first paragraph because the specification allegedly fails to provide a sufficient written description or an enabling disclosure. The Applicants respectfully submit that the claims are allowable under §112 in light of the above amendments and for at least the following reasons.

The claims stand rejected under 35 U.S.C. §112 first and second paragraphs, for indefiniteness and containing new matter. The Applicants assert that these rejections are addressed by the above amendments.

Regarding the Examiner's concerns over "an animal-specific antibody" as recited in claim 25, the selective antibody against the human TSH receptor is coated on the solid phase via an non-selective animal-specific antibody, i.e. an antibody (antiserum) which binds immunoglobulins of the animal used for the production of the selective antibody to the human TSH receptor. Therefore, the "animal-specific antibodies" are used to immobilize the antibodies selectively binding the hTSHR ("the immobilized selective antibody").

The claims stand rejected under 35 U.S.C. §103(a) as unpatentable over Vitti *et al* (Acta med Austriaca 23(1-2):52-6, 1996) or US 5,614,363, each in view of Harlow *et al* (in Antibodies A laboratory Manual, Cold Spring Harbor Laboratory 1988, pp. 556, 564-91), Nicholson *et al* (J Mol Endocrinol 16(2): 159-70, 1996), and/or Morgenthaler *et al* (J Clin Endocrinol Metab 81(2): 700-6, 1996). Additionally, the claims stand rejected as obvious over US 5,814,461 ('461), in view of US 5,614,363 Harlow *et al*, Nicholson *et al*, or Morgenthaler *et al*. The Applicants respectfully traverse these rejections for at least the following reasons.

Any combination of Vitti et al. or US Pat No. 5,614,363 in view of Harlow *et al.*, Nicholson *et al.* and /or Morgenthaler *et al.* is based on impermissible hindsight and does not render the present invention obvious. The Examiner admits that the primary references do not provide a "method for the determination of TSH receptor autoantibodies comprising immobilized affinity purified recombinant human TSH receptor to a solid support by an antibody against the receptor." Paper No. 18, page 10. In an attempt to remedy this shortcoming the Examiner cites secondary references which fail to demonstrate why the

skilled artisan would have been motivated to combine them with the primary references, or even that such a combination would work.

For example, nowhere in Harlow is there any mention of a binder that would be sufficient to bind the recombinant human TSH receptor to a solid support while still remaining functional in the claimed method. How could the skilled artisan be expected to look to a general textbook and select this specific binder, when even the art cited by the Examiner indicates that prior attempts to immobilize TSH receptors *met with failure*? *See* US 5,814,461, Col. 2, lines 64-57.

Still more tangential is the work of Nicholson *et al.*, which discusses attempts to express recombinant TSH receptors in insect cells and E. coli. The obtained TSH receptors and receptor fragments were not functional TSH receptors (i.e. they did not compete with TSH and/or were not active in cell stimulation tests). Furthermore, neither the obtained receptors or receptor fragments, or the antibodies obtained when said receptors or receptor fragments were used for immunization purposes, were ever successfully used in a solid phase assay for human TSH receptor autoantibodies in a biological fluid.

Finally, '461 does not render the present invention obvious. The '461 patent discusses a method which, as cited above, acknowledges the difficulties of designing a solid phase assay for the determination of TSH receptor autoantibodies, and therefore sets out to ***avoid*** such a procedure. Any combination of references with the '461 patent must, therefore, change the principle by which Bergmann operates. Such a substantial change is specifically forbidden. *See* MPEP § 2143.02 (citing *In re Ratti* 270 F.2d 810, 123 USPQ 349 (CCPA 1959)). Under similar facts, the *Ratti* Court applied the following rationale in reversing the Examiner's obviousness rejection:

> [the] suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate. Id at 813.

Accordingly, the Applicants respectfully request reconsideration and withdrawal of this rejection.

In view of the foregoing, the claims are now believed to be in form for allowance, and such action is hereby solicited. If any point remains in issue which the Examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number listed below.

All objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: _____

Paul L. Sharer
Registration No. 36,004
Direct No. (703) 905-2180

PLS/CMB
1600 Tysons Boulevard
McLean, VA 22102
(703) 905-2000 Telephone
(703) 905-2500 Facsimile

Attorney Reference: 011377/0263260